

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A study protocol for a single-blind, randomized controlled trial to evaluate clinical effects of an Integrated Qigong exercise intervention on freezing of gait in Parkinson's disease
AUTHORS	Li, Zhenlan; Zhuang, Jie; Jiang, Yan; Xiao, Guiping; Jie, Kuncheng; Wang, Tian; Yin, Wenhan; Zhang, Yu; Wang, Zhen

VERSION 1 – REVIEW

REVIEWER	Gammon M. Earhart Washington University in St. Louis
REVIEW RETURNED	15-Jan-2019

GENERAL COMMENTS	<p>This paper describes the protocol for a randomized, controlled study of Health Qigong among people with Parkinson's disease (PD) who have freezing of gait (FOG). The following concerns should be addressed to enhance the manuscript:</p> <p>Major Concerns</p> <ol style="list-style-type: none">1. There is a lack of specificity within the text regarding the specific outcome measures to be used. Saying that the primary focus is on gait parameters and FOG is not sufficient. Please clarify exactly what outcome measures will be used (e.g. table suggests that gait speed and stride length as well as a FOG questionnaire will be used).2. More information is needed about the interventions. Are the sessions done individually or in a group? How will the Qigong be personalized to each individual? This seems a key point of the rationale for the study but no information is presented about the process or algorithms that will be used to customize the experience for each participant.3. Address the fact that the control group will have much less contact time than the other groups. Why is this not being controlled for to account for the impact of attention/social interaction? This mismatch in exposure seems like an unnecessary confound. <p>Minor Concerns</p> <ol style="list-style-type: none">1. Please use people-first language throughout, e.g. instead of saying Parkinson's disease patients use the term people with Parkinson's.2. Editing for grammar/English is needed.3. Clarify which version of FOG questionnaire will be used - is it the FOGQ or the NFOGQ.4. It would be helpful to have information about participants' living situation and physical activity levels at baseline.5. Why go to the trouble of doing a full 3-D kinematic analysis with 45 markers if the desired outcomes are only speed and a stride length?
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REVIEWER	Kim Delbaere UNSW, Australia
REVIEW RETURNED	10-Feb-2019

GENERAL COMMENTS	<p>The paper is well-written and my comments are to improve clarity in certain sections:</p> <ol style="list-style-type: none"> 1. Eligibility: Inclusion criterion is to have had at least 1 fall in the past 12 months. However, the demographics reports on falls in the past 6 months. Inclusion criteria and demographics table should match. Also, do you have any exclusion criteria for people who have had an excessive number of falls in the past 6 months? Or similarly, people with very high number of FOG episodes? 2. Power calculation: An attrition rate of 10% is very low and quite possibly not realistic. 3. Randomisation: Will you apply stratification to ensure the 3 groups have similar FOG levels. 4. Medication use: Within the description of the balance exercise study arm, the authors state: "The participants in the balance exercise group will follow their regular medication scheme and perform balance exercise in their medication stage." Does the same apply for the Qigong group? 5. Heart rate monitor: Within the description of the Qigong study arm, the authors state: "The heart rate of all the participants will be monitored by Polar-team2 (Polar Electro, Finland) during training." What is the reason for this? And why is this unique to the Qigong group (and not for the balance group)? 6. Control group: The control group will get monthly phone calls. Please specify what will be discussed. Will there be a standard protocol for this? 7. Statistical analyses: How will you deal with missing data? <p>Overall, the manuscript needs a good proofread for English. While it is well-written, there are a few errors throughout. Also, please write the methods in future tense.</p>
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REVIEWER	Pieter Ginis KU Leuven Belgium
REVIEW RETURNED	13-Feb-2019

GENERAL COMMENTS	<p>The manuscript describes a study protocol for a single blind RCT study in which the authors aim to compare Health Qigong with balance training and a no intervention control group in people with freezing of gait and investigate which intervention is most effective to reduce FOG and Falls. The research question is clinically very relevant and it is thus a worthwhile endeavor from the authors. However, I have some comments on the proposed protocol manuscript which have to be addressed before publication. I hope that my remarks aid the authors' paper.</p> <ol style="list-style-type: none"> 1. My main concern is that I miss the in-depth rationale why the authors hypothesize that Health Qigong is the most beneficial intervention for FOG and Falls. As I now read it, Health Qigong is a dynamic balance training while the balance training described is much more static balance oriented. Hence, what is the added value of health Qigong? Does it specifically targets one of the core underlying aspects of FOG and Falls? E.g. FOG has been linked with deficits such as motor-adaptation, cognitive-switching,
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	<p>impulsive behaviour,... Is there an inherent aspect of Health Qigong that targets one or more of this aspects?</p> <p>2. Have the article checked for English grammar. Now many times the authors write will instead of will be.</p> <p>3. In the abstract, specify the gait parameter that will be selected for primary outcome.</p> <p>4. Will the dosage of training and attention be equal in the three interventions? It should be mentioned in the abstract and is not adequately handled in the manuscript. Now it seems that the control group will have much less contacts with the study personal, this may induce bias.</p> <p>5. In the abstract it is mentioned that all participants or their guardians signed the informed consent. Why refer to the guardians? No infants or highly demented people will be included normally? I assume that all participants are able to sign the ICF themselves.</p> <p>6. In similar vein as comment 1, Tai Chi is well explained and the difference it holds with Health Qigong, however, what Health Qigong consists of is not clearly explained. In the discussion some of the exercises are explained, but this should be handled in the introduction in my opinion.</p> <p>7. page 7 line 119-120 is not clear if it reflects to Tai Chi or to Health Qigong.</p> <p>8. Page 8 line 151 UK Brain Bank, not simply UK</p> <p>9. Is the FOGQ used, why not the NFOGQ?</p> <p>10. Why are people with DBS excluded from the study? Provide a rationale for this.</p> <p>11. For the Sample size calculation, which outcome parameter was used and what were the absolute values on which the 35% effect size was estimated.</p> <p>12. Page 10: Listing of the twelve Health Qigong forms without explanation does not provide information. Perhaps make it in a table with figures or pictures to visualize the tasks.</p> <p>13. The tasks will be personalized, this is a good aspect, but is there any type of guideline or decision matrix made beforehand to sort of standardize this procedure?</p> <p>14. It is not clear if all exercises are performed once in a sequence first then following a break performed a second time, or are the exercises done twice before going to the next one and if the break is just after 20 minutes.</p> <p>15. Page 11 line 210 mentions 40min of Health Qigong, or balance, while it should be 45min (20min + 5min rest + 20min).</p> <p>16. Are balance and health Qigong training done in individual sessions or in group sessions? In case of group sessions, there may be a difference in attention per participant, which induces bias to the study. Furthermore, it should be described how large the groups are.</p> <p>17. Page 11 line 215 mentions explicitly that the balance exercise group follows their regular medication scheme and perform balance exercise in their medication stage. Is this ON medication? I hope this is also the case for the Health Qigong group?</p> <p>18. Describe how the trainings of both Health Qigong and Balance exercise will evolve over the study period. New exercises added? Longer duration? Adding dual tasks?</p> <p>19. Falls are a primary outcome of the study. Looking at previous studies, the sample size is relatively small. For instance when comparing it to the V-TIME study of Mirelman et al. I assume the sample size calculation is not performed on this outcome.</p> <p>20. At baseline, you will collect Falls retrospectively and compare this to the monitored results during the study and follow-up period.</p>
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	<p>This induces a large bias in your study as the results retrospectively (at baseline) may be a under- or overestimation of the actual falls rate. It should first have included a baseline fall recording period before randomization into one of the three groups.</p> <p>21. It is insufficiently described how the authors will handle the fall recording at follow-up. During the training period there is regular contact to check it, but what during the follow-up period, will the authors send regular reminders. Wasn't it an option to do falls monitoring with a sensor? Or do online falls diary, so that the researchers can be alerted if a patient did not fill in his diary on a daily basis. This should have had much more thought a-priori and should be detailed extensively in the protocol.</p> <p>22. Page 19 line 320-321: How will the burden of the intervention be assessed?</p> <p>23. Page 19 line 325: SPSS reference is missing information.</p> <p>24. As mentioned above, part of the exercise explanation should be detailed in the methods and their core principle making it unique for FOG and Falls should be handled in the introduction. Here in the discussion I would want to read what the contribution of the outcomes will give to the clinical and research field. Will it add evidence pro- or contra earlier findings? This while the future perspective from page 21 line 377 onwards regarding fMRI and fNIRS is irrelevant in this manuscript. It can be given as a suggestion to look at underlying findings/differences that are first found or not found behaviorally. Thus, in the discussion of the RCT outcome manuscript.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Major Concerns

1. We added gait velocity, stride length, and stride time variability in the Page19, line438-439, as well as listed them in the abstract and Table2 (Page22). These parameters reflects the gait dysfunction and fall risk more than other elements of gait base on the previous references.(Lin C C, et al., Lord S, et al., Harrison EC, et al).
2. The interventions will be conducted in group-based exercise. At beginning of training, we will instruct participants to perform different movement requirements according to functional level. The range of motion of each movement will be reduced for participants with rigidity. The pace of movement will be decreased for participants with bradykinesia. The later stage, participants will perform movement at entire range of motion as much as possible. The revised version will be detailed in Line 348-353, Page14.
3. We added group session and interaction each week and health education once a month to increase contact time and attention for control group (Line 388-390, Page 15).

Minor Concerns

1. We appreciate the reviewer's attention to detail, and we have corrected the term as suggested, used "individuals with PD" or "people with PD".
2. Thank you for your suggestion. We have reedited for English grammar in revised version.
3. Base on your suggestion, we will use NFOG questionnaire, it is developed largely based on freezing of gait (FOG-Q), more accuracy than previous version in evaluating severity of FOG. The modification can be found in Line 445, Page 19) .
4. Base on your suggestion, we added "self-report habitual physical activity" 、 "family situation" in the revised manuscript. The detail version can be found in Line 413 and 416(page 16) and table 1.
5. When we first design our study, our team conceived the protocol according to the equipment

available in our laboratory, it has strong spatial and temporal motion capture abilities and accurate in gait analysis. At present, we also have instrumented computerized walkway (GAIRite, CIR, System Inc., Franklin, NJ), which contribute to our data collection, so we will apply it for gait analysis in our study.

Reviewer: 2

1. We changed the inclusive criteria, at least 1 fall over the 6 months math to the demographics. We will use self-report fall and follow the definition of falling to exclude people who have had an excessive number of falls based on the definition of fall. For people with high number of FOG episodes, we will use the score of NFOG.
2. We have changed attrition rate to 15% according to your suggestion, the revised version can be found in Line 284, page 11.
3. We will apply the stratified random sampling method by stage of the disease(H&Y stage) (Line 290, Page 11).
4. Both Qigong group and balance training group will follow their medication scheme throughout the study period, we have described it on Line 303, Page 12.
5. We're sorry to miss this important information, the heart rate of balance exercise group also will be monitored by Polar-team2, it will help us to control training intensity and reduce risk during exercise. The revised version can be found Line 311-312, Page 12.
6. We will ask participant "physical activity situation, the progression of disease, medication, health status, psychological status", the revised version can be found in Line 396-397, Page 16.
7. An intention-to-treat analysis will be used to deal with missing data. We have described it in line 520-522.

Reviewer: 3

1. Qigong integrates both static and dynamic exercises with a great emphasis on regulating breath, and exercising intrinsic control and mental intent. Qigong exercise is characterized by trunk rotation, bending and extending at waist and movement of limbs both medial-laterally and anterior-posteriorly, all driven by the core of the body. The exercise involves postural demanding movements such as single leg standing and chirographic and manipulative moving postures. The detail explanation can be found in Line 174-182, Page 7.
2. Thank you for your reminding. We have checked all the English grammar and corrected tense.
3. We have added the stride length, gait velocity, and stride time variability, the revision can be found in Line 60, page 2.
4. We appreciate the reviewer's attention to detail. We have modified this part based on your suggestion; the Qigong group and balance exercise group keep consistent contact time in intervention (Line 306-311, Page 12). In control group, we added group session per week. The revised version can be detailed in Line Line 388-391, Page 15.
5. In China, most of people with Parkinson's disease need guardians to accompany them to engage in training program for safety concerns, some participates complain that they have been not written since they suffered from the disease, the tremor or stiffness affect them to hold a pen, so their guardians help them to sign informed consent.
6. We have corrected base on your suggestion, added the rational of Qigong exercise targeted FOG improvement and fall prevention. We have put the explanation of Qigong exercise in the introduction, 174-182, Page 7.
7. This sentence reflect the characteristic of Tai Chi movement.
8. We have corrected it to UK Brain Bank criteria, Line 247-248(Page 10).
9. Our study will use NFOG questionnaire, it is developed largely based on freezing of gait questionnaire (FOG-Q), more accuracy than previous version in evaluating severity of FOG.
10. We primarily consider the impact of DBS on motor symptom severity, and safety concern. We

need to focus on if something goes wrong with the stimulator when participant perform exercise. They usually consult the clinician to adjust the simulator during training. Previous study suggested that subthalamic nucleus (DBS-STN) can significant increase length and variability of walking bouts emerged, as well as improve the diversity and flexibility of walking pattern.(Rochester L , et al.) This may affect our study outcome, so we exclude participant with DBS surgery.

11. Thank you for your advice. We recalculated the sample size by detect the difference of stride length and the score of FOG from baseline to the end of intervention. The revised version can be found in Line 272-273, 282-283, Page 11.

12. We provided Qigong forms picture, and shown them in Figure 2.

13. Thank you for your advice. We'll individualize the exercise base on functional limitation of each participant, including the intensity, frequency, time, the difficulty of movement. Detailed information can be found in Line 347-353, Page 14.

14. It takes 20 minutes to complete a set of Health Qigong exercise with 12 forms, 6 repetitions for each form. 5 minutes break after the preform a set of exercise, we also permit participants take a break based on their own condition, but they need to meet training requirement in each training session.

15. We have corrected the training process, a complete set Health Qigong will be performed in about 20 minutes, the participants will perform twice, 5 minutes break intervals. The revised version can be detailed in Line 308-311, page 12.

16. Both balance training group and Qigong group will perform group-based exercises, they will divided into small group, a group size is 10-15 people. A trained instructor in each group will teach participants and correct movement for individual during every training session in order to ensure the attention and contact time of each participant. Line 306-308, Page 12.

17. Both balance training group and Qigong group will follow their medication scheme through the study period. The revised version will be detailed in Line 303, Page 12.

18. The participants in Qigong group will perform the single form at beginning, accompany with multiple repetitions, the instructor will help them review previous learned movement in each training session. New movement will be added progressively during training period. At later stage, participants will practice consecutively the entire exercise(Line 343-357, Page 13-14).

Balance training will be progressed according to principle of balance training(Line 380-383, Page 15). Dual-task will not be added in the training protocol, but we will consider adding the dual-task training in our future study.

19. We totally agree with you, we calculated sample size on the basis of gait parameters like stride length.

20. We changed the fall recording period to have a fall over the past 6 months to ensure the collection of fall data, a blind assessor will collect the fall rate based on participants' self-report fall and definition of falling.

21. The fall recording at follow-up will adopted fall dairy, monthly phone interview, and self-report from the end of follow-up. The detailed correction are listed in Line 469-474, Page 20.

22. The burden will be assessed by their through face-to-face interview, involving medical and physical condition, exercise safety (Line 507).

23. Thank you for reminding. We have added the SPSS reference information in the revised version.

24. The results of this study will add evidence to support the benefit of Qigong on improvement of walking ability and reduction of fall risk in people with PD. The results will proved that Integrated Qigong exercise might be a supplementary therapy to manage gait disorder and fall prevention for clinician and therapist. The revision can be found in Line 598-601, Page 29-30.

VERSION 2 – REVIEW

REVIEWER	Gammon M. Earhart Washington University in St. Louis
REVIEW RETURNED	03-Apr-2019

GENERAL COMMENTS	The authors revised their manuscript extensively based on the first round of reviews, and the work is improved as a result. However, there are some concerns that have not been fully addressed. For example, the control group that receives education is still not adequately matched for time/attention as they are only getting 1/3 the amount of engagement as the training groups. Thorough editing for English is still needed.
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REVIEWER	Kim Delbaere NeuRA, Australia
REVIEW RETURNED	12-Apr-2019

GENERAL COMMENTS	The authors have revised the paper well and I have no further comments.
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REVIEWER	Pieter Ginis KU Leuven Belgium
REVIEW RETURNED	24-Apr-2019

GENERAL COMMENTS	<p>I would like to congratulate the authors with this improved protocol paper. Almost all of my previous comments have been addressed. However, I still have some comments which may help the readability of the manuscript.</p> <ol style="list-style-type: none"> 1. Please verify the tenses used, it regular shifts from future to past tense. Also have the text checked for other English grammar. 2. Seen the group size, 10 - 15 people, of the training and only one therapist I fear that not enough attention will be given to the individual patient. If we compare this with a recent balance study Conradson et al. 2012, who had group sizes of 5-7 patients with 2 physiotherapists present. 3. The previous comment would also relate to have an exclusion criteria of a maximal number of falls in the previous period for safety reasons. However, this may impede the study outcomes drastically. 4. My previous comment why patients with DBS are excluded from the study is not addressed yet. 5. What is the rationale for the heart rate recording during the training sessions. The balance exercises do not seem to be at the level that physical intensity has to be controlled. In case it will be used during the training, please specify how this will be handled. 6. The title suggests that it will look at the effect on freezing of gait. Then I would expect that the primary outcome be selected as FOG or at least as a FOG proxy measure (rapid full turns) as mentioned by Zach et al. 2015 or Mancini et al. 2017. Now the primary outcome is both gait, then kept open if it will be gait speed, gait variability, step length and in the second paragraph mentioned as FOG. Please be as specific as possible which exact feature will be the primary outcome and why it is selected. In similar vein, report that this outcome is used for the sample size calculation as that is not explicitly done still. 7. Related to the previous remark and because of the inclusion criteria of NFOGQ>1, it is inconsistent to read that 'participants
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	<p>with freezing will be instructed to perform transferring and stepping while maintaining postural stability', suggesting that also non-freezers will be included. I assume the authors were referring to the moments at which the participants experience a FOG episode during the training? Please clarify this part.</p> <p>8. Seen that two of the training interventions focus on balance it is very odd to observe that no balance assessment is included as a secondary outcome of the study.</p> <p>9. I assume that a more sophisticated statistical model will have to be applied such as a generalized linear mixed model, which can take into account the missing values while the repeated measures ANOVA in SPSS automatically deletes all participants who have a missing value at one of the timepoints. Unless the authors will use an approach with data imputation, but then they need to mention which imputation strategy they will use. Furthermore, there are also limits to the percentage of data that may be imputed if missing values are in the study. Also, please list which potential covariates you foresee and if you either significant nor insignificantly different between the groups will take into the analysis. For example, correcting for age, disease duration, LEDD, cognitive ability.</p> <p>10. In the discussion the authors mention that postural control deficiency is due to the excessive trunk movement and this causes falls. This may be one of the reasons, but is certainly not the only reason. Please be more nuanced in the story and put it in perspective with other potential causes of falls in PD.</p> <p>11. No study limitations have been addressed and how the authors will attempt to deal with the possible limitations.</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer 1

Response: We have already add contact time and attention for control group. They received 60-min group session per week, health education every four weeks over the intervention period, and phone follow-up twice per month.

(Line 234-240). We have carefully edited the English.

Reviewer 2

No further comments.

Reviewer 3

Response:

- 1.Thank you. We have carefully corrected the English grammar.
- 2.We have change it into two trained instructors to provide adequate instructional attention.
- 3.We accept your advice and delete the criteria.

4. We excluded patient with DBS for safety concern. Patient need to adjust the stimulator and change the battery during postoperative follow-up, the stimulator may be unstable and interfere with the experimental task, so we excluded PD patient with DBS.

5. During the training duration, the difficult level is increased progressively by adjusting intensity, amplitude, frequency, so we need to monitor the heart rate. Detailed information can be found in Line 193.

6. We explained why we select the gait speed, stride length and stride time variability, and FOG as primary outcome, and cite reference, Line 275-291. Although FOG proxy measure (rapid full turns) can provoke the occurrence of FOG, it cannot reflect the patient experience freezing episodes throughout intervention period, so we select NFOG-Q to detect and assess the incidence and severity of FOG except during intensive training period. The sample size was also calculated base on the FOG(Line 153).

7. We have modified according to your advice, clarify the participants experience FOG episode during training.

8. We added Mini-BESTest as a balance measurement, the detail information can be found in Line 303-307.

9. Thank you for your advice, we added a linear mixed model to analyze missing value. The disease duration(H&Y) and cognitive ability(MoCA) as covariance, these variables may differ significantly between groups. The revision can be found in Line 357-360.

10. We explained the causes of falls in PD, impaired protective postural response and postural adjustment in preparation for stepping increase risk of fall. The revision version can be found in Line 374-375.

11. We added several limitations, included blind to participants cannot be achieved, and limitation of selection on patient for disease severity and geographic area, the revised version can be found in 393-398.